Table 3. The association between total energy intake and all-cause mortality in 3,373 men and 4,331 women aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
Men						
No. of participants	674	675	674	675	675	
No. of death	299	259	228	217	247	
Model 1	1.00 (reference)	0.97 (0.82-1.15)	0.95 (0.80-1.13)	0.92 (0.77-1.10)	1.12 (0.94-1.32)	0.448
Model 2	1.00 (reference)	0.99 (0.84-1.17)	0.95 (0.80-1.13)	0.95 (0.79-1.13)	1.11 (0.93-1.32)	0.452
Model 3	1.00 (reference)	1.07 (0.90-1.28)	1.11 (0.91-1.36)	1.18 (0.94-1.48)	1.45 (1.12-1.86)	0.008
Women						
No. of participants	863	869	866	865	868	
No. of death	270	234	188	187	160	
Model 1	1.00 (reference)	1.03 (0.86-1.23)	0.97 (0.80-1.17)	1.01 (0.84-1.23)	0.88 (0.72-1.08)	0.295
Model 2	1.00 (reference)	1.04 (0.87-1.24)	0.97 (0.80-1.17)	1.02 (0.85-1.24)	0.89 (0.73-1.09)	0.344
Model 3	1.00 (reference)	1.07 (0.88-1.30)	0.99 (0.79-1.23)	1.04 (0.81-1.32)	0.90 (0.68-1.20)	0.527

P for linear trend values were calculated as a categorical variable.
Model 1 was adjusted for age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤ 20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), and work position (management, professional, and other).
Model 2 was adjusted for variables in Model 1 plus body mass index (< 18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥ 30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no).
Model 3 was adjusted for variables in Model 2 plus fish intake (quartile category), meat intake (quartile category), vegetable intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

sional, and other). Data on physical activity were not collected.

To account for the potential effect of subclinical disease on baseline dietary intake (e.g., undiagnosed cancer), analyses were repeated after excluding subjects who had died within the first 3 years (n=55), 5 years (n=108), and 10 years (n=321) after baseline.

All hypothesis tests were two sided and based on a 0.05 level of significance.

Results

Baseline Characteristics by Quintiles of Total Energy Intake

The baseline characteristics of study participants according to the sex-specific quintiles of total energy intake are shown in **Table 1**. As compared with Q1, participants in Q5 were younger and heavier for both sexes. Mean BMI was higher for men in Q5 but similar across the quintiles in women. Never smoker in men and women and current drinker in men were more prevalent in Q5. Intake of fish, meat, vegetable, fruit, carbohydrate, fat, protein, and sodium were significantly higher in Q5 for both sexes. In women, systolic blood pressure values and proportion of antihypertensive drug users were significantly lower in Q5.

All-Cause Mortality by the Quintiles of Total Energy Intake

Over 29 years of follow-up, we observed 2,289 deaths (1,250 men and 1,039 women). **Table 2** shows person-year totals, numbers of all-cause deaths, and HRs of all-cause mortality with 95% CIs according to the quintiles for total energy intake categories.

We observed no consistent association between the total energy intake and all-cause mortality. In Model 3, the HR for all-cause mortality was 1.17 (95%CI: 0.97−1.41, *P* for linear trend=0.146). After further exclusion of participants who died during the first 3, 5, or 10 years of follow-up, we also observed a similar association (data not shown).

After stratification by sex, we observed significant increases in the risk of all-cause mortality in only men (**Table 3** and **Supplemental Table 1**). In Model 3, the HR for all-cause mortality was 1.45 (1.12−1.86, *P* for linear trend=0.008) in men and 0.90 (0.68−1.20, *P* for linear trend=0.527) in women. These trends were also observed in all strata after further stratification by age, smoking, drinking, type of work, type of position, and BMI except for never smokers in men (**Table 4**). Among never smokers, we observed no association between the total energy intake and all-cause mortality.

In **Supplemental Table 2**, we examined which

Table 4. Stratified analyses of the association between total energy intake and all-cause mortality in 3,373 men aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
Men						
Age						
<50 years						
No. of death	67	60	60	64	79	
Model 3	1.00 (reference)	0.93 (0.64-1.35)	0.94 (0.62-1.42)	1.16 (0.73-1.85)	1.57 (0.94-2.61)	0.068
≥50 years						
No. of death	232	199	168	153	168	
Model 3	1.00 (reference)	1.14 (0.93-1.40)	1.20 (0.95-1.51)	1.15 (0.88-1.50)	1.39 (1.04-1.86)	0.055
Smoking						
Never						
No. of death	41	26	37	31	29	
Model 3	1.00 (reference)	0.68 (0.40-1.16)	1.01 (0.57-1.78)	0.91 (0.48-1.70)	0.93 (0.46-1.91)	0.974
Ever						
No. of death	258	233	191	185	218	
Model 3	1.00 (reference)	1.12 (0.93-1.36)	1.12 (0.90-1.40)	1.20 (0.94-1.54)	1.50 (1.14-1.96)	0.008
Drinking						
Never						
No. of death	70	49	47	26	36	
Model 3	1.00 (reference)	0.90 (0.60-1.36)	1.03 (0.65-1.65)	0.85 (0.46-1.55)	1.39 (0.72-2.68)	0.502
Ever						
No. of death	229	210	180	191	211	
Model 3	1.00 (reference)	1.11 (0.91-1.36)	1.12 (0.89-1.41)	1.22 (0.95-1.56)	1.46 (1.11-1.93)	0.012
BMI						
≥18.5 kg/m^2, <25.0 kg/m^2						
No. of death	224	209	164	168	178	
Model 3	1.00 (reference)	1.06 (0.86-1.29)	1.01 (0.80-1.28)	1.13 (0.87-1.47)	1.28 (0.96-1.72)	0.119
≥25.0 kg/m^2						
No. of death	39	36	43	40	60	
Model 3	1.00 (reference)	1.21 (0.74-1.98)	1.85 (1.08-3.17)	1.52 (0.84-2.74)	2.99 (1.53-5.83)	0.005
Type of work						
Blue collar						
No. of death	202	168	149	130	166	
Model 3	1.00 (reference)	1.15 (0.92-1.43)	1.28 (1.00-1.63)	1.23 (0.92-1.64)	1.63 (1.20-2.22)	0.004
White collar						
No. of death	95	84	78	87	81	
Model 3	1.00 (reference)	0.94 (0.68-1.31)	1.02 (0.70-1.47)	1.15 (0.78-1.70)	1.29 (0.81-2.05)	0.210
Work position						
Management or professional						
No. of death	125	102	88	105	97	
Model 3	1.00 (reference)	0.95 (0.72-1.25)	1.00 (0.73-1.37)	1.14 (0.82-1.61)	1.32 (0.89-1.95)	0.154
Other						
No. of death	173	156	140	112	150	
Model 3	1.00 (reference)	1.14 (0.89-1.44)	1.16 (0.89-1.52)	1.17 (0.86-1.61)	1.53 (1.09-2.14)	0.029

P for linear trend values were calculated as a categorical variable.
Model 1 was adjusted for age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), and work position (management, professional, and other).
Model 2 was adjusted for variables in Model 1 plus body mass index (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no).
Model 3 was adjusted for variables in Model 2 plus fish intake (quartile category), meat intake (quartile category), vegetable intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

items enhanced the association between the total energy intake and mortality. Point estimates increased most strongly after adjustment of vegetable intake, especially in men. In **Supplemental Table 3**, we further cross-classified participants into groups according to vegetable intake categories. All-cause mortality increased in the category of high total energy and low vegetable intake in both men and women.

Cause-Specific Mortality by the Quintiles of Total Energy Intake

Table 5 shows the numbers of cause-specific deaths, and HRs of cause-specific mortality with 95% CIs according to the quintiles of total energy intake.

The association of total energy intake with cancer mortality was a significant trend in men (*P* for linear trend=0.038). The point estimate of Q5 was 1.45 (95%CI; 0.90−2.34, *P* for linear trend=0.112) for CVD mortality in men. We could not conduct a stratified analysis of age, smoking, drinking, type of work, type of position, and BMI for cause-specific mortality because of the small number of events.

We further examined the association of total energy intake with types of CVD mortality, such as CHD, heart failure, stroke, cerebral infarction, and cerebral hemorrhage. In comparison with Q1, the Model 3 in Q5 was increased for CHD mortality in men (HR; 2.63, 95%CI; 0.95−7.28, *P* for linear trend=0.016) and women (HR; 2.91, 95%CI; 1.02−8.29, *P* for linear trend=0.032). The point estimate of Q5 was 1.74 (95%CI; 0.72−4.19, *P* for linear trend=0.377) for cerebral infarction in men.

Discussion

Our study indicates that there is a consistent association in men and no consistent association in women between the total energy intake and all-cause mortality over a long period in Japanese recruited from 300 areas across the nation. In particular, the risk of CHD mortality in both sexes and cancer mortality in men significantly increased with the highest total energy intake. The present study was the first to investigate the association between the total energy intake and mortality in populations living in Asia. Additionally, we estimated individual total energy intake based on the weighing record method for 3 consecutive days in each household[21, 22, 27]. This method is based on actual intake and used to estimate absolute rather than relative intakes of energy[37]. This is an important strength of our study compared with studies using food frequency questionnaires. Moreover, individual total energy intake values generated using our household-based weighing record method showed a high correlation with values generated using an individual-based weighing record method (r=0.94)[28].

Previous studies showed a U shaped or no association between the total energy intake and all-cause mortality[8-10]. The present study showed a significant association between the total energy intake and all-cause mortality in men, but its association showed a non-significant association in women. One of the reasons for this sex difference might be due to the effect of sirtuin[7]. Kanfi *et al.* also showed that transgenic mice that overexpressed sirtuin 6 had a significantly longer lifespan than wild-type mice in males only[38]. Meanwhile, Leosdottir *et al.* showed a U shaped association[8] stating that a possibility of increased mortality in participants with low energy intake was attributable to undetected chronic disease associated with diminished appetite. However, their follow-up period was short (mean: 6.6 years), suggesting that their results were largely affected by death in the early period.

In Model 3, we additionally adjusted for fish, meat, vegetable, and fruit intake. The effect of these food items on the association between the total energy intake and mortality has not been investigated in previous studies. We examined which items enhanced the association between the total energy intake and mortality (**Supplemental Table 2**). As a result, the point estimate remarkably increased after adjustment for vegetable intake, especially in men. Several studies have shown that a lower mortality risk is associated with a higher vegetable intake, including previous our study, which had a same dataset as that of the present study[18, 39-42]. An increase in total energy intake also increases vegetable intake because of the increase in absolute intake. An inconsistent association between the total energy intake and all-cause mortality in previous studies might be due to a higher vegetable intake in the higher energy intake group. In fact, after further cross-classification of participants into groups according to vegetable intake categories, we observed an excess risk of mortality in the high total energy intake and low vegetable intake category in men and women (**Supplemental Table 3**).

It seems that a significant increase in CHD risk in both sexes and cancer risk in men contributed for all-cause mortality in participants with a high energy intake. Although impact of higher saturated fat intake and hypercholesterolemia on CHD among Japanese populations have been reported[43, 44], previous studies on total energy intake have shown either no association or an inverse association with CVD mortality or incidence[8, 11-14]. The reasons for the observed inconsistency between the previous studies and ours are

Table 5. The association between total energy intake and cause specific mortality in 7,704 participants aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
Men						
Cancer mortality						
No. of death	105	104	88	104	99	
Model 3	1.00 (reference)	1.19 (0.89-1.59)	1.20 (0.86-1.67)	1.47 (1.03-2.10)	1.50 (0.999-2.24)	0.038
Cardiovascular disease						
No. of death	89	61	69	54	71	
Model 3	1.00 (reference)	0.89 (0.63-1.26)	1.18 (0.81-1.73)	1.09 (0.70-1.69)	1.45 (0.90-2.34)	0.112
Coronary heart disease						
No. of death	18	8	12	17	16	
Model 3	1.00 (reference)	0.66 (0.28-1.58)	1.41 (0.59-3.34)	2.40 (0.97-5.97)	2.63 (0.95-7.28)	0.016
Heart failure						
No. of death	10	9	8	7	7	
Model 3	1.00 (reference)	0.94 (0.35-2.57)	1.21 (0.39-3.72)	0.95 (0.27-3.41)	0.95 (0.23-3.92)	0.983
Stroke						
No. of death	41	36	35	20	36	
Model 3	1.00 (reference)	1.06 (0.65-1.71)	1.15 (0.67-1.98)	0.71 (0.36-1.38)	1.22 (0.62-2.42)	0.886
Cerebral infarction						
No. of death	25	20	22	9	20	
Model 3	1.00 (reference)	1.18 (0.63-2.21)	1.59 (0.80-3.17)	0.78 (0.31-1.96)	1.74 (0.72-4.19)	0.377
Cerebral hemorrhage						
No. of death	8	9	6	6	11	
Model 3	1.00 (reference)	0.98 (0.35-2.79)	0.65 (0.19-2.27)	0.66 (0.17-2.54)	1.02 (0.25-4.12)	0.866
Women						
Cancer mortality						
No. of death	76	86	61	67	54	
Model 3	1.00 (reference)	1.32 (0.94-1.85)	1.10 (0.74-1.64)	1.22 (0.80-1.87)	1.00 (0.61-1.64)	0.905
Cardiovascular disease						
No. of death	92	76	51	70	58	
Model 3	1.00 (reference)	1.08 (0.77-1.51)	0.83 (0.56-1.25)	1.33 (0.88-2.00)	1.16 (0.72-1.88)	0.386
Coronary heart disease						
No. of death	18	17	10	16	14	
Model 3	1.00 (reference)	1.47 (0.71-3.04)	1.16 (0.48-2.84)	2.52 (1.05-6.04)	2.91 (1.02-8.29)	0.032
Heart failure						
No. of death	22	15	9	16	13	
Model 3	1.00 (reference)	0.75 (0.36-1.56)	0.50 (0.20-1.25)	0.83 (0.35-1.96)	0.73 (0.26-2.04)	0.637
Stroke						
No. of death	44	30	23	18	26	
Model 3	1.00 (reference)	0.84 (0.50-1.41)	0.70 (0.39-1.27)	0.60 (0.30-1.21)	0.82 (0.39-1.71)	0.389
Cerebral infarction						
No. of death	26	17	15	8	10	
Model 3	1.00 (reference)	0.96 (0.48-1.92)	1.20 (0.55-2.59)	0.79 (0.29-2.15)	1.19 (0.41-3.45)	0.887
Cerebral hemorrhage						
No. of death	10	6	4	6	9	
Model 3	1.00 (reference)	0.50 (0.17-1.50)	0.25 (0.07-0.93)	0.35 (0.10-1.30)	0.36 (0.09-1.45)	0.178

P for linear trend values were calculated as a categorical variable.
Model 3 was adjusted for age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), work position (management, professional, and other), body mass index (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no), fish intake (quartile category), meat intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

unclear.

There are differences between these previous studies and the present study. First, the Japanese have a different dietary pattern than Western populations, and their dietary pattern contains a higher amount of sodium[45]. High energy intake correlates with an increase in sodium, and high sodium intake might cause hypertension. Thus, increasing CVD mortality in participants with high total energy intakes might be affected by hypertension incidence during the follow-up period, although we adjusted for systolic blood pressure and antihypertensive drug use at the baseline. Second, SES including education, occupational class, and poverty are factors associated not only with mortality but also with health-seeking behaviors and inequalities in health[46-48]. Moreover, in the past, people who were of low SES had low total energy intakes[49, 50]. In previous studies, it is possible that the effect of caloric restrictions on lower mortality might be canceled because of higher mortality in low SES participants with low energy intakes and lower mortality in high SES participants with high energy intakes.

Several limitations of our study should be considered. First, total energy intake was measured only at baseline. Therefore, we were unable to account for possible changes in total energy intake over the follow-up period. Second, we could not adjust for energy expenditure-related variables, such as physical activity, which is associated with total energy intake, because we did not have information about physical activity[51]. However, after the results were stratified by the type of work, we observed similar associations between white-collared and blue-collared participants. Therefore, the lack of adjustment for physical activity in our study may have underestimated the mortality risk in participants with high energy intake because higher levels of physical activity were reported to be associated with lower mortality[52]. Third, we estimated individual total energy intake based on the weighing record method for 3 consecutive days in each household[21, 22, 27, 28]. Even though there is a possibility of a systematic error, a previous study showed that individual estimates obtained from household-based weighed records, which is the same method as ours, were highly correlated with those obtained by the individual-based weighed record method in total energy intake (Pearson's correlation coefficients: $r=0.90$)[28]. Thus, the high validity of estimation for individual intake was confirmed. Additionally, the estimated values may not reflect the long-term usual intake. However, Nakamura *et al.* has shown that our dietary estimates method showed fairly good agreement with individual food frequency questionnaires[23]. Fourth, we did not have information about menopausal status and history of cancer, which associates with both total energy intake and mortality, possibly causing a source for reverse causality. However, we observed similar results after the exclusion of participants who died during the first 3, 5, or 10 years of follow-up, respectively. Fifth, for a surrogate measure for SES and/or physical activity, we were able to use only "type of work" and "work position" from the data. We acknowledge that this measure may not capture SES and physical activity well; thus, residual confounding may exist in our findings.

In conclusion, we observed a significant association between the high energy intake, all-cause mortality and cancer mortality among men, and CHD mortality among all participants over a long period in a general Japanese population. Particularly, low vegetable and high energy intake might be a risk factor of mortality. After adjustment for food items, especially vegetables, these findings partly support the animal evidence and imply that caloric restriction might also decrease mortality in humans.

Whether control of food consumption is a useful means for lowering the risk of death, especially CHD, warrants further study. However, underweight due to low energy intake is one of the important public health problems in Japanese elderly and women. The present study did not examine the association between the caloric restriction and mortality but rather the association between the total energy intake and mortality. Further intervention studies are needed to confirm the benefit of caloric restriction.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Contributions

MN, AF, TO, and KM contributed to the design of the study. TO, KM, NO, TH, KY, YA, NM, NT, AK, YM, TO, AO, and HU participated in data collection. MN, AF, TO, KM, YM, and RDA participated in data analysis. MN, AF, TO, and KM participated in the writing of the report. All authors participated in critical revision of the manuscript and approved the final version of the report for submission.

Appendix

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Abbreviations List

SES: socioeconomic status, NIPPON DATA: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, NNSJ: the National Nutrition Survey in Japan, BMI: body mass index, ICD: the International Classification of Diseases and Related Health Problems, CVD: cardiovascular diseases, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ANOVA: analysis of variance, SD: standard deviation,

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Supplemental Table 1.
Stratified analyses of the association between total energy intake and all-cause mortality in 4,331 women aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
Women						
Age						
< 50 years						
No. of death	43	41	36	44	33	
Model 3	1.00 (reference)	1.04 (0.66-1.63)	0.66 (0.40-1.12)	0.77 (0.45-1.34)	0.59 (0.31-1.14)	0.098
≥ 50 years						
No. of death	227	193	152	143	127	
Model 3	1.00 (reference)	1.09 (0.88-1.34)	1.06 (0.83-1.36)	1.10 (0.84-1.44)	1.01 (0.74-1.38)	0.892
Smoking						
Never						
No. of death	209	192	170	165	139	
Model 3	1.00 (reference)	1.06 (0.86-1.31)	1.05 (0.82-1.33)	1.07 (0.83-1.39)	0.92 (0.68-1.24)	0.714
Ever						
No. of death	61	41	18	22	20	
Model 3	1.00 (reference)	1.31 (0.81-2.13)	0.92 (0.50-1.71)	0.92 (0.46-1.83)	1.15 (0.51-2.60)	0.909
Drinking						
Never						
No. of death	211	190	155	149	128	
Model 3	1.00 (reference)	1.11 (0.89-1.38)	1.02 (0.80-1.31)	1.09 (0.83-1.42)	0.90 (0.66-1.24)	0.614
Ever						
No. of death	59	41	33	38	31	
Model 3	1.00 (reference)	0.93 (0.59-1.47)	0.92 (0.55-1.54)	0.90 (0.52-1.56)	0.99 (0.52-1.88)	0.886
BMI						
≥ 18.5 kg/m^2, < 25.0 kg/m^2						
No. of death	170	163	124	108	98	
Model 3	1.00 (reference)	1.12 (0.88-1.43)	1.09 (0.83-1.44)	1.02 (0.74-1.40)	0.87 (0.61-1.24)	0.416
≥ 25.0 kg/m^2						
No. of death	78	51	48	68	47	
Model 3	1.00 (reference)	0.86 (0.58-1.26)	0.81 (0.52-1.26)	1.05 (0.68-1.62)	0.84 (0.49-1.44)	0.899
Type of work						
Blue collar						
No. of death	226	194	155	151	133	
Model 3	1.00 (reference)	1.07 (0.87-1.32)	0.97 (0.76-1.23)	1.03 (0.79-1.34)	0.87 (0.64-1.19)	0.423
White collar						
No. of death	36	32	30	30	21	
Model 3	1.00 (reference)	1.19 (0.70-2.03)	1.06 (0.58-1.94)	1.28 (0.67-2.45)	1.14 (0.53-2.44)	0.672
Work position						
Management or professional						
No. of death	20	21	18	15	10	
Model 3	1.00 (reference)	1.66 (0.76-3.63)	1.76 (0.74-4.21)	1.12 (0.43-2.89)	0.86 (0.29-2.54)	0.528
Other						
No. of death	246	209	169	170	150	
Model 3	1.00 (reference)	1.04 (0.85-1.28)	0.95 (0.75-1.20)	1.01 (0.78-1.30)	0.89 (0.66-1.19)	0.463

P for linear trend values were calculated as a categorical variable.
Model 1 was adjusted for age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤ 20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), and work position (management, professional, and other).
Model 2 was adjusted for variables in Model 1 plus body mass index (< 18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥ 30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no).
Model 3 was adjusted for variables in Model 2 plus fish intake (quartile category), meat intake (quartile category), vegetable intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

Supplemental Table 2. The association between total energy intake and all-cause mortality in 7,704 participants aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
No. of participants	1,537	1,544	1,540	1,540	1,543	
Person-years	38,445	39,684	40,311	40,705	40,779	
No. of deaths	569	493	416	404	407	
Model 2	1.00 (reference)	1.02 (0.90-1.15)	0.97 (0.85-1.10)	0.98 (0.86-1.12)	1.02 (0.90-1.16)	0.991
+ Meat intake	1.00 (reference)	1.01 (0.90-1.15)	0.97 (0.85-1.10)	0.97 (0.85-1.11)	1.01 (0.88-1.15)	0.820
+ Fish intake	1.00 (reference)	1.01 (0.89-1.14)	0.96 (0.85-1.10)	0.97 (0.85-1.11)	1.02 (0.89-1.16)	0.957
+ Vegetable intake	1.00 (reference)	1.09 (0.96-1.23)	1.07 (0.93-1.24)	1.11 (0.95-1.30)	1.20 (1.01-1.42)	0.065
+ Fruit intake	1.00 (reference)	1.03 (0.92-1.17)	1.00 (0.88-1.14)	1.02 (0.89-1.17)	1.07 (0.93-1.22)	0.469
+ Sodium intake	1.00 (reference)	1.03 (0.91-1.17)	1.00 (0.87-1.14)	1.01 (0.88-1.16)	1.05 (0.92-1.21)	0.621
+ Meat, fish, vegetable, fruit, and sodium intake	1.00 (reference)	1.08 (0.95-1.23)	1.07 (0.92-1.24)	1.10 (0.93-1.30)	1.17 (0.97-1.41)	0.146
Men						
Model 2	1.00 (reference)	0.99 (0.84-1.17)	0.95 (0.80-1.13)	0.95 (0.79-1.13)	1.11 (0.93-1.32)	0.452
+ Meat intake	1.00 (reference)	0.99 (0.83-1.17)	0.95 (0.79-1.13)	0.94 (0.78-1.13)	1.09 (0.91-1.31)	0.591
+ Fish intake	1.00 (reference)	0.98 (0.83-1.16)	0.93 (0.78-1.12)	0.93 (0.77-1.12)	1.09 (0.91-1.30)	0.607
+ Vegetable intake	1.00 (reference)	1.09 (0.92-1.30)	1.12 (0.92-1.37)	1.20 (0.97-1.50)	1.49 (1.18-1.89)	0.002
+ Fruit intake	1.00 (reference)	1.02 (0.86-1.21)	1.00 (0.83-1.19)	1.00 (0.83-1.21)	1.18 (0.99-1.42)	0.138
+ Sodium intake	1.00 (reference)	1.01 (0.85-1.19)	0.98 (0.82-1.17)	0.98 (0.81-1.18)	1.15 (0.95-1.39)	0.270
+ Meat, fish, vegetable, fruit, and sodium intake	1.00 (reference)	1.07 (0.90-1.28)	1.11 (0.91-1.36)	1.18 (0.94-1.48)	1.45 (1.12-1.86)	0.008
Women						
Model 2	1.00 (reference)	1.04 (0.87-1.24)	0.97 (0.80-1.17)	1.02 (0.85-1.24)	0.89 (0.73-1.09)	0.344
+ Meat intake	1.00 (reference)	1.03 (0.87-1.23)	0.96 (0.79-1.16)	1.01 (0.84-1.23)	0.88 (0.72-1.08)	0.291
+ Fish intake	1.00 (reference)	1.04 (0.87-1.24)	0.97 (0.80-1.17)	1.03 (0.85-1.25)	0.91 (0.74-1.11)	0.422
+ Vegetable intake	1.00 (reference)	1.07 (0.89-1.30)	1.00 (0.81-1.24)	1.05 (0.83-1.32)	0.92 (0.71-1.20)	0.604
+ Fruit intake	1.00 (reference)	1.05 (0.88-1.26)	0.98 (0.81-1.19)	1.04 (0.86-1.27)	0.91 (0.74-1.12)	0.493
+ Sodium intake	1.00 (reference)	1.06 (0.88-1.26)	0.99 (0.81-1.20)	1.05 (0.86-1.28)	0.91 (0.74-1.13)	0.517
+ Meat, fish, vegetable, fruit, and sodium intake	1.00 (reference)	1.07 (0.88-1.30)	0.99 (0.79-1.23)	1.04 (0.81-1.32)	0.90 (0.68-1.20)	0.527

P for linear trend values were calculated as a categorical variable.

Model 2 was adjusted for sex, age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), work position (management, professional, and other), body mass index (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no).

Supplemental Table 3.
The association between total energy intake, vegetable intake, and all-cause mortality in 7,704 participants aged 30-69 years

	Vegetable intake (g/day)		
	Q1	Q2	Q3
Total energy intake (kcal/day)			
Q1			
No. of participants	1,773	632	162
No. of death	609	231	63
HRs	1.00 (reference)	0.98 (0.83-1.15)	0.99 (0.75-1.30)
Q2			
No. of participants	685	1,234	649
No. of death	171	338	210
HRs	1.01 (0.85-1.20)	1.02 (0.88-1.19)	0.93 (0.77-1.11)
Q3			
No. of participants	109	702	1,758
No. of death	41	166	460
HRs	1.76 (1.28-2.43)	1.01 (0.84-1.22)	0.94 (0.81-1.11)
Men			
Q1			
No. of participants	789	273	62
No. of death	345	107	24
HRs	1.00 (reference)	0.94 (0.75-1.19)	0.86 (0.56-1.33)
Q2			
No. of participants	288	544	292
No. of death	107	178	102
HRs	1.06 (0.85-1.32)	0.90 (0.74-1.11)	0.87 (0.67-1.12)
Q3			
No. of participants	47	308	770
No. of death	22	111	254
HRs	1.80 (1.16-2.81)	1.06 (0.84-1.34)	0.92 (0.74-1.14)
Women			
Q1			
No. of participants	984	359	100
No. of death	264	124	39
HRs	1.00 (reference)	1.00 (0.79-1.26)	1.07 (0.75-1.53)
Q2			
No. of participants	397	690	357
No. of death	64	160	108
HRs	0.92 (0.70-1.22)	1.16 (0.93-1.44)	0.98 (0.76-1.28)
Q3			
No. of participants	62	394	988
No. of death	19	55	206
HRs	1.71 (1.06-2.76)	0.92 (0.68-1.26)	0.93 (0.73-1.18)

HRs was adjusted for sex, age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤ 20 cigarettes/day, and current smoker > 20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), work position (management, professional, and other), body mass index (< 18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥ 30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no), fish intake (quartile category), meat intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

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BRIEF COMMUNICATION

Relationship of type of work with health-related quality of life

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Abstract
Purpose To examine the relation of work type with health-related quality of life (HRQoL) in healthy workers.
Methods We cross-sectionally examined 4427 (3605 men and 822 women) healthy workers in Japan, aged 19–69 years. We assessed HRQoL based on scores for five scales of the SF-36. Multiple regression was applied to examine the relation of work type (nighttime, shift, day to night, and daytime) with the five HRQoL norm-based scores, lower scores of which indicate poorer health status, adjusted for confounding factors, including sleeping duration.
Results Shiftwork was inversely related to role physical [regression estimate (β) = −2.12, 95 % confidence intervals (CI) −2.94, −1.30, $P < 0.001$], general health ($\beta = -1.37$, 95 % CI −2.01, −0.72, $P < 0.001$), role emotional ($\beta = -1.24$, 95% CI −1.98, −0.50, $P < 0.001$), and mental health ($\beta = -1.31$, 95% CI −2.01, −0.63, $P < 0.001$) independent of confounding factors, but not to vitality. Day-to-nighttime work was inversely related to all the five HRQoL subscales (*P*s 0.012 to <0.001).
Conclusion Shiftwork was significantly inversely related to four out of the five HRQoL, except for vitality, and day-to-nighttime work was significantly inversely related to all five HRQoL, independent of demographic and lifestyle factors.

Keywords Shift work · Health-related quality of life · SF-36

For HIPOP-OHP Research Group.

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Introduction

Shiftwork has long been known to disrupt circadian rhythm, sleep, and work–life balance [1]. A higher incidence of coronary heart disease, metabolic syndrome, mental and behavioral disorders, and sleep disturbances has been observed among shift workers [2–5]. Previous cross-sectional studies have reported that shiftwork and day-to-night work strongly impaired quality of life (QOL) [6–12]. However, these studies were mostly done in female nurses, QOL was not comprehensively evaluated, and important confounders, such as sleep duration, were not considered. The main purpose of the present cross-sectional study was to examine the relationship of work types as an exposure

Table 1 Characteristics of participants by group according to the work type—HIPOP-OHP study 1999–2000

Type of work	Daytime	Nighttime	Shift	Day to night	*P*
Characteristics					
Person *N*	3094	73	1017	243	
Age (years)	42.6 ± 8.9	50.8 ± 6.8†	37.9 ± 10.1†	40.1 ± 9.7†	<0.001
% among total women	86.7	0.1*	9.3†	3.9†	<0.001
Role physical	49.6 ± 9.1	49.2 ± 9.9	48.1 ± 11.1†	45.8 ± 12.3†	<0.001
General health	48.0 ± 8.6	49.2 ± 10.2	46.2 ± 9.23†	45.8 ± 8.8†	<0.001
Vitality	46.3 ± 9.0	49.2 ± 11.6*	45.1 ± 9.3†	43.9 ± 9.6†	<0.001
Role emotional	50.1 ± 9.3	50.7 ± 9.0	49.0 ± 10.9†	47.0 ± 11.3†	<0.001
Mental health	47.5 ± 9.1	49.9 ± 10.0	45.8 ± 9.6†	44.5 ± 10.2†	<0.001
BMI (kg/m^2)#	22.8 ± 0.1	22.4 ± 0.4	23.3 ± 0.1†	23.4 ± 0.2†	<0.001
Alcohol (ml/day)	20.8 ± 30.0	29.1 ± 40.3	22.4 ± 35.3	17.1 ± 26.0	0.012
Ex-smoker (%)	17.5	24.7	15.1	14.8	0.073
Current smoker (%)	60.4	49.3	39.6†	50.6*	<0.001
IPAQ4 (%)	1.1	4.2*	2.3†	2.5*	0.001
Sleep (h)	6.40 ± 0.85	6.47 ± 1.09	6.46 ± 1.07	6.15 ± 1.06†	<0.001

Values are shown as mean ± SD or mean ± SE (for BMI). Characteristics of participants by group according to work type in 4427 Japanese men and women in 1999–2000 are shown. NBS HRQoL was used

BMI body mass index, *IPAQ* International Physical Activity Questionnaire classification, *NBS* norm-based scoring scores

* $P < 0.05$; † $P < 0.01$ compared to daytime work

with health-related QOL (HRQoL) measured with SF-36 as the outcome-dependent variables adjusted for confounding factors in a large-scale database of healthy workers in Japan.

Participants and methods

We analyzed baseline data from the high-risk and population strategy for occupational health promotion (HIPOP-OHP) study, the details of which have been described elsewhere [13–15]. In brief, the study population consisted of full-time workers at 12 large-scale companies throughout Japan in 1999–2000. The present study examined 4427 participants (3605 men and 822 women), aged 19–69 years (mean ± SD 41.6 ± 9.6 years) who underwent a physical examination and a lifestyle survey. Informed consent was obtained from each participant. Approval for the study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 10–16).

The study protocol was standardized according to the manual of the HIPOP-OHP research group [13]. The spare time physical activity of each participant was converted into metabolic equivalent (MET) minutes/week according to the International Physical Activity Questionnaire (IPAQ) [16]. Participants were classified into four classes of physical activity: class 1–4 at thresholds of 600, 1500, and 3000 MET minutes/week. Drinkers were defined as those consuming more than 1.25 ml (1 g) of ethanol a day. The average alcohol intake (ml) per day was obtained for each participant [14]. Smoking status was obtained.

Five subscales of SF-36

We used version 2.0 of the SF-36 questionnaire form and scoring program [17–19]. We used five out of eight subscales that were available in the HIPOP-OHP dataset: role physical, general health, vitality, role emotional, and mental health, because the HIPOP-OHP study was basically conducted for healthy workers with no physical disabilities [13]. Each domain is scored on a scale of 0–100, with lower scores indicating poorer health status. We used standardized domain scores using Japanese population norms to give a mean score of 50 and a standard deviation of 10 [norm-based score (NBS)] [18–20].

The Chi-square test was used to compare dichotomous variables between the work types, followed by a post hoc application of logistic analysis compared to the daytime work. A one-way analysis of variance was used to compare means between the groups, followed by a post hoc application of Dunnett's test compared to the daytime work when $P < 0.05$. Cohen's d was calculated for effect size index, when difference in HRQoL was significant compared to daytime work. BMI was standardized by age and gender, and analysis of covariance was used for

Table 2 Work type and health-related quality of life—results of multiple regression analysis—HIPOP-OHP study 1999–2000

Variable	Role physical		General health		Vitality		Role emotional		Mental health	
	β	95 % CI	*β*	95 % CI	*β*	95 % CI	*β*	95 % CI	*β*	95 % CI
All participants (N = 4427)										
R^2	0.023		0.054		0.074		0.016		0.038	
Night vs daytime	−0.41	−2.91, 2.10	1.75	−0.28, 3.80	1.71	−0.38, 3.80	0.08	−2.32, 2.48	1.58	−0.60, 3.76
Shift vs daytime	*−2.11*†	*−2.89, −1.34*	*−1.37*†	*−2.02, −0.72*	−0.61	−1.27, 0.05	*−1.24*†	*−1.98, −0.50*	*−1.31*†	*−2.01, −0.63*
Day to night vs daytime	*−3.51*†	*−4.89, −2.13*	*−1.47*†	*−2.63, −0.32*	*−1.55**	*−2.74, −0.37*	*−2.56*†	*−3.88, −1.24*	*−2.34*†	*−3.57, −1.12*

Results of analyses by multiple regression analysis to examine the relation of work type with NBS HRQoL (role physical, role emotional, general health, vitality, and mental health) adjusted for lifestyle factors and other factors, including age, sex (man = 1, woman = 0), alcohol consumption (ml/day), IPAQ classification (IPAQ2 to IPAQ4 vs IPAQ1), sleep hours, smoking status (ex-smoker, current smoker, and never smoker). R^2 for regression model, *β* with 95 % confidence intervals are also shown

Italic values indicate statistical significance at the 5 % level

β regression coefficient, *IPAQ* International Physical Activity Questionnaire classification

* $P < 0.05$; † $P < 0.01$

comparison. Multiple regression was applied to examine the relation of work type (nighttime, shift, day to night, and daytime) with the five HRQoL, adjusted for confounders, including age, sex (man = 1, woman = 0), alcohol consumption (ml/day), IPAQ classification (IPAQ2 to IPAQ4 vs IPAQ1), sleep hours, smoking status (ex- and current smoker, and never smoker). Significant interaction terms with age and gender with other variables (age × ex- and current smoking in general health, age × IPAQ in vitality and mental health) were entered. The interactions between the work type and gender/age were not statistically significant. Spearman's correlations between the five HRQoL and the canonical correlations of background characteristics associated with the linear combination of the five subscales of HRQoL were obtained. All *P* values were two-sided, and $P < 0.05$ was considered significant. All analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC).

Results

Among 4427 men and women, 3094 were in daytime work, 73 in fixed night work, 1017 in shiftwork, and 243 in day-to-night work. With effect size (f^2): 0.15, power level: 0.80, number of predictors: 6, probability level: 0.05, the sample size required was estimated to be 97. Characteristics of participants by work type are given in Table 1. There were fewer women in the groups other than the daytime work group. The mean age, vitality, and the percentages of IPAQ4 were larger in fixed nighttime work compared to daytime work. The four other HRQoL in fixed nighttime work were not different compared to daytime work. Compared to daytime work, the mean age, all five HRQoL, and the percentage of current smokers in the shiftwork were lower, while the mean BMI was larger. Compared to daytime work, the mean age, all five HRQoL, sleep hours, and the percentage of current smokers in the day-to-night work group were lower, while the percentages of IPAQ4 were larger. Percentage of ex-smoker was not different between four work type groups. Cohen's *ds,* obtained when difference in HRQoL was significant compared to daytime work, were between 0.1 and 03. All these indicated small effect sizes.

The results of multiple regression analysis are shown in Table 2 and Fig. 1. Fixed night work was related to none of the five HRQoL scores, as compared to daytime work, probably due to small number of participants in this group. Compared to daytime work, shiftwork was significantly inversely related to role physical, general health, role emotional, and mental health, but not related to vitality. Compared to daytime work, day-to-night work was significantly inversely related to all five HRQoL scores.

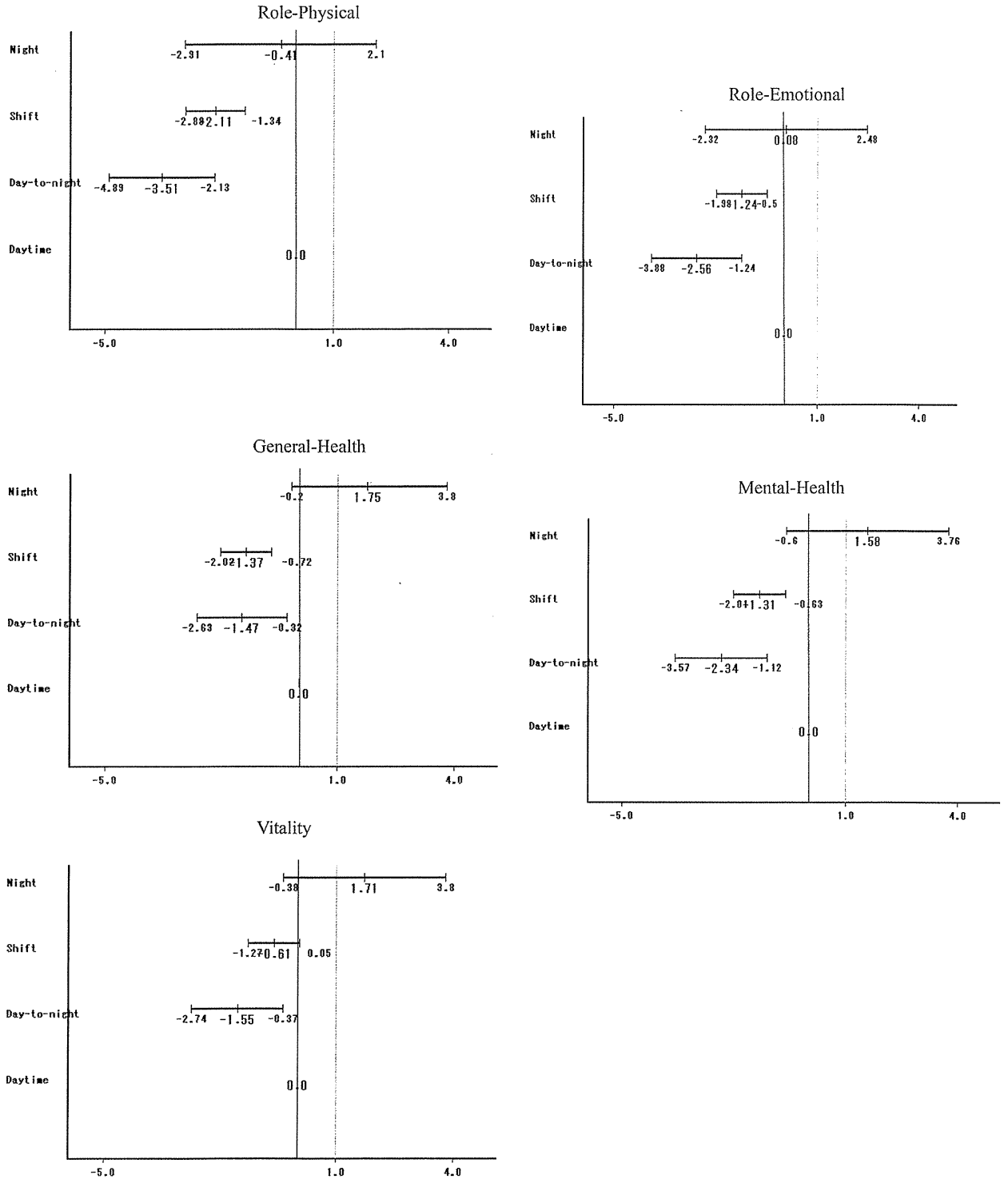

Fig. 1 Coefficients for five subscales of HRQoL for night vs day; shift vs day; and day-to-nighttime vs day adjusted for covariates and their associated confidence intervals are shown

Spearman's correlations between the five HRQoL and the canonical correlations of background characteristics associated with the linear combination of the five subscales of HRQoL are given in Table 3. Spearman's correlations between the five HRQoL were good. All the canonical correlations were statistically significant.

Table 3 Spearman's correlation coefficients and canonical correlations

	General health	Vitality	Role emotional	Mental health
Spearman's correlation coefficients				
Role physical	0.300	0.323	0.647	0.353
P	<0.001	<0.001	<0.001	<0.001
General health		0.497	0.298	0.451
P		<0.001	<0.001	<0.001
Vitality			0.366	0.661
P			<0.001	<0.001
Role emotional				0.499
P				<0.001

	Cor	Adj Cor	Eigenvalue	*E* proportion	*E* cumulative	*P*
Canonical correlations						
1	0.300	0.297	0.099	0.780	0.780	<0.001
2	0.133	–	0.018	0.142	0.922	<0.001
3	0.080	–	0.007	0.051	0.973	<0.001
4	0.058	–	0.003	0.027	1	0.005

Spearman's correlations and *P* values between five subscales of HRQoL are shown in the upper panel, and the canonical correlations of background characteristics associated with the linear combination of the five subscales of HRQoL are shown in the lower panel

Cor canonical correlation, *Adj Cor* adjusted canonical correlations, *E* eigenvalue

Discussion

In the present study, we found that shiftwork was significantly inversely related to four out of the five HRQoL, except for vitality, while day-to-night work was significantly inversely related to all five HRQoL, independent of demographic and lifestyle factors.

Several previous studies showed the effect of shiftwork on physical and mental health. Coffery et al. [6] showed overall job performance was lower, and job-related stress was higher in rotating shift nurses compared to nurses in other work types. Driesen et al. [7] showed that men and women involved in shiftwork were associated with a higher prevalence of depressed mood. Gordon et al. [8] showed that compared to men working non-variable work schedules, those who were working variable shifts exhibited higher rates of heavy drinking, job stress, and emotional problems. On the other hand, Skipper et al. [9] showed that shiftwork was not significantly related to either nurses' physical health or mental depression.

Nakata reported that full-time employees working >10 h per day, sleeping <6 h per day, or reporting insufficient sleep were positively associated with depression [10] and risk of workplace injury [11], but inversely associated with self-rated health scale [12]. He emphasized that longer working hours with shorter sleep or insufficient sleep exerted synergistic undesirable associations with the above conditions. Our analysis included sleep hours, and we found that day-to-night work was significantly inversely related to all five HRQoL, compared to daytime work, independent of sleeping duration. Thus, factors other than sleep disturbance may be operating in the inverse relation of day-to-night work with HRQoL.

The disruption of circadian rhythm and impairment of sleep associated with shiftwork have been shown to generate physical and mental health problems. Melatonin and glucocorticoids may be linked to an adverse psychosocial work environment and to irregular work schedules [21]. Furthermore, social contacts are more difficult to maintain and familial relationships are impaired due to families' constant attempts to adapt to changing daily rhythms and this may interfere with the adaptation to shiftwork and protect from undesirable outcomes [21].

The strengths of the present study include being population based, large scale, and multisite with highly standardized methods. Thus, the findings are likely to be generalizable to middle-aged Japanese. However, the present study has some limitations. First, the present study was limited by its cross-sectional design. Some workers might have been left because of a variety of reasons, and thus, the sample may not be representative. Second, key variables such as socioeconomic status are missing. Third, the sample size of women was small. We need further studies in women with sufficient number of participants. Fourth, observed differences in HRQoL subscales between work types were relatively small in relation to the currently

discussed minimum importance difference for the SF-36 dimensions [22].

In conclusion, shiftwork was significantly inversely related to four out of five HRQoL, except for vitality, and day-to-night work was significantly inversely related to all five HRQoL in a large-scale database of mostly male healthy workers in Japan, independent of demographic and lifestyle factors. Wherever possible, these two work types should be avoided.

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Interaction of Blood Pressure and Body Mass Index With Risk of Incident Atrial Fibrillation in a Japanese Urban Cohort: The Suita Study

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BACKGROUND AND PURPOSE
To prevent stroke, strategies for atrial fibrillation (AF) prevention and an early detection of AF by electrocardiogram are essential. However, only a limited prospective studies have examined the risk factors for AF, even in blood pressure (BP) and body mass index (BMI), which are not clear among general populations. We investigated the impacts of BP and BMI on the risk of incident AF in a general population.

METHODS
A total of 6,906 participants (30–84 years) in the Suita Study were prospectively followed up for incident AF. Participants were diagnosed with AF if AF or atrial flutter was present on an electrocardiogram from a routine health examination (every 2 years) or if AF was indicated as a present illness from health examinations and/or medical records during follow-up. Adjusted Cox proportional hazard ratios (HRs) were calculated.

RESULTS
During the 12.8-year follow-up, 253 incident AF events occurred. Compared with the systolic BP (SBP) < 120 mm Hg and normal-weight, the adjusted HRs (95% confidence intervals; CIs) of incident AF in the systolic hypertension and the overweight (BMI ≥ 25 kg/m^2) groups were 1.74 (1.22–2.49) and 1.35 (1.01–1.80), respectively. Compared with SBP < 120 mm Hg and normal weight, the adjusted HRs (95% CIs) of incident AF in the SBP = 120–139 mm Hg with overweight and the systolic hypertension with normal or overweight were 1.72 (1.01–2.91), 1.66 (1.10–2.50), and 2.31 (1.47–3.65), respectively (*P* for interaction = 0.04).

CONCLUSIONS
Systolic prehypertension and overweight are associated with incident AF in Japanese population. The association between SBP and AF may be evident by overweight.

Keywords: atrial fibrillation; blood pressure; body mass index; hypertension; prospective cohort study; risk factor.

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Atrial fibrillation (AF) is the most common chronic arrhythmia and is a risk factor for all-cause mortality[1] and stroke.[2] To prevent stroke, strategies for AF prevention and an early detection of AF by electrocardiogram are essential. However, only a limited number of prospective studies have examined the risk factors for AF among general populations.

Recent studies have gradually revealed that not only hypertension,[3,4] but also prehypertension is a risk factor for incident AF.[5,6] Pulse pressure is also a risk factor for incident AF.[7] However, it is still difficult to determine which blood pressure (BP) categories associated with incident AF in prospective studies.[8] It may be dependent on the different backgrounds of populations, lifestyles, and/or cardiovascular risk factors[9] such as obesity.

Positive associations with incident AF have been observed for overweight[10] and class 1[11,12] or 3[13] obesity. These different results may depend on the different backgrounds of the study populations. The combined impact of obesity and should also be considered regarding the incidence of AF. However, few prospective studies have examined the combined effect of BP and BMI on the incidence of AF in a general population. Only the Women's Health Study showed no interaction between hypertension and obesity in incident AF.[14] Different populations may have different incidence rate of AF,[15] and therefore possibly different risk factors for AF. Here, we assessed the hypothesis that the combination of BP and BMI categories increases the risk of incident AF in an urban general Japanese population, which has higher BP and less obesity than Westerners.[9]

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METHODS

Study participants

The design and selection criteria of the Suita Study have already been described.[16] As a baseline, 12,200 and 3,000 participants (aged 30–79 years) were randomly selected from the municipality population registry of Suita city and stratified into groups by sex and age in 10-year increments in 1989 and 1996, respectively. Of these, participants attending the baseline examination of the original cohort (n = 6,485; 1989–1996) and the secondary cohort (n = 1,329; 1996–1998) were eligible for the present investigation. In addition, the baseline examination of a volunteer group (n = 546, 1992–2006) was also included in the present study. Informed consent was obtained from all participants. These evaluations are referred to as the baseline examination for the present investigation. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Suita, Japan.

We excluded participants for the following reasons: prior or current illness of AF or atrial flutter (n = 42) at baseline, missing covariate (n = 2), and failure to complete the baseline examination (n = 2) or the follow-up health surveys (n = 1,408), resulting in a sample of 6,906 participants.

Blood pressure and physical measurement

In National Cerebral and Cardiovascular Center, well-trained physicians measured each participant's BP 3 times using a mercury column sphygmomanometer, an appropriate-size cuff, and a standard protocol.[16] Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. BP values were taken as the average of the second and third measurements, which were recorded more than 1-minute apart. At the time of the baseline examination, each participant was classified into 1 of 3 BP categories (normal BP (<120/80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/90 mm Hg and/or antihypertensive drug use)). If the systolic BP (SBP) and diastolic BP (DBP) readings for participants were in different categories, the participants were categorized into the higher of the 2 BP categories. SBP and DBP alone categories were as follows: normal (<120/80 mm Hg), systolic and diastolic prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/90 mm Hg including antihypertensive drug users), respectively. Categories of body mass index (BMI), calculated as weight (kg) divided by height (m) squared, were defined by the following criteria: underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), and overweight (≥25 kg/m^2).[17]

Biochemical measurement and questionnaire

At the baseline examination, we performed routine blood tests that included serum total cholesterol and glucose levels. Hypercholesterolemia was defined as total cholesterol levels ≥5.7 mmol/L or current use of antihyperlipidemic medications. Diabetes (DM) was defined as fasting serum glucose ≥7.0 mmol/L, nonfasting serum glucose ≥11.1 mmol/L, or medications for DM. Physicians and nurses administered questionnaires covering personal habits and present illness. Past/present illness of stroke included cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Past/present illness of heart disease included coronary heart disease, valvular disease, and chronic heart failure. Premature contractions consisted of frequent atrial, junctional, and/or ventricular premature beats (Minnesota Code 8-1-1, 8-1-2, or 8-1-3) without AF/flutter at the baseline. The glomerular filtration rate (mL/min/1.73 m^2) of each participant was calculated using the Modification of Diet in Renal Disease equation modified by the Japanese coefficient (0.881), as follows: glomerular filtration rate = $0.881 \times 186 \times (\text{age})^{-0.203} \times (\text{serum creatinine})^{-1.154}$ (×0.742 for women).[18] Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73m.^{2}

Definition of AF and follow-up

Standard 12-lead electrocardiograms were obtained from all participants in the supine position. Each record was coded independently using the Minnesota Code by 2 well-trained physicians. Participants were diagnosed with AF if AF (Minnesota Code 8-3-1) or atrial flutter (Minnesota Code 8-3-2) was present (n = 170) on an electrocardiogram from the routine Suita health check-up examination (every 2 years) or if AF was indicated as a present illness by the health check-up examination (n = 46), and hospital medical records (n = 33), and/or death records (n = 4) during follow-up. The end point of the follow-up period for each participant was whichever of the following options occurred first: (i) the date of the first AF event, (ii) date of the last health examination and medical records, and (iii) May 31, 2013 (censored).

Statistical analysis

We examined the association between BP or BMI categories and the risk of incident AF using multivariable-adjusted Cox proportional hazard regressions after adjusting for sex and age in 5-year increments as stratified variables, BMI (underweight, normal weight, and overweight) or BP (normal BP, prehypertension, and hypertension), and other potential confounding factors at the baseline survey: namely, hypercholesterolemia, DM, and current smoking and drinking, respectively (Model 1). For Model 2, further confounding variables were used for cohort groups, chronic kidney disease, histories of stroke, coronary heart disease, chronic heart failure, and premature contractions in addition to those in Model 1 (Model 2). The Cox proportional hazard ratios (HRs) and 95% confidence intervals (95% CI) were fitted to the combination of the BP and BMI categories after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors. We tested for interactions term generated by SBP × BMI strata in the Cox model adjusting for Model 2. We tested for interactions between follow-up year and BP or BMI to determine whether the assumption of proportional hazards for prediction of AF was valid. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the study participants grouped according to the SBP and BMI categories are presented in Table 1. At the baseline survey, the participants with systolic hypertension and overweight tend to be older, had higher prevalence of DM and hyperlipidemia, histories of stroke and heart disease, and had a lower frequency of current smoking compared to the participants with normal SBP and underweight, for both men and women. The baseline characteristics according to the 3 cohort groups (original, secondary, and volunteer) are shown in Supplementary Table I, which provides the details of participants' baseline characteristics.

During the 12.8 years of follow-up, 253 incident AF events occurred. There was no interaction between follow-up year and BP for prediction of AF in the primary Cox model, suggesting that the proportional hazards assumption was appropriate. Compared with the normal ranges of BP categories and pulse pressure <40 mm Hg, the risks of incident AF were increased in the participants with systolic and diastolic hypertension, hypertension, and pulse pressure ≥60 mm Hg, respectively adjusting for age and sex, and Models 1 and 2 (Table 2). Systolic hypertension is a risk factor of AF in men (HR = 1.65 and 95% CI = 1.07–2.56) and women (HR = 1.93 and 95% CI = 1.03–3.65, data not shown). After further adjustment by DBP, a significant association was still observed in systolic hypertension (HR = 1.74 and 95% CI = 1.12–2.69). However, the influences of DBP and pulse pressure were attenuated after adjustment for SBP. When antihypertensive medication users were classified into their BP levels, the risks of AF according to BP categories were similar (Model 2-adjusted HRs and 95% CI in SBP: 1.72 and 1.20–2.48 for systolic hypertension, data not shown).

Compared with the normal weight participants, the adjusted risks of incident AF were increased in the overweight participants after adjustment for age and sex, in Models 1 and 2, and even after adjustment for both SBP and DBP (Table 3).

After adjustment in Model 2, each 1-unit increase in SBP, DBP, pulse pressure, and BMI were associated with increases in the risk of AF. Among BP variables, after the further adjustment by BPs, only SBP was observed to increase the risk of AF (Table 4). The results in men and women separately were weak due to the small sample sizes, but were marginally or statistically significant (Supplementary Table II). After the adjustment by Model 2 plus SBP and DBP, a 5% increased risk of incident AF by 1 kg/m^2 increase in BMI was revealed.

Compared with SBP < 120 mm Hg and normal weight, the adjusted HRs (95% CIs) of incident AF in the SBP = 120–139 mm Hg participants with overweight and the systolic hypertension participants with normal weight or overweight were 1.72 (1.01–2.91), 1.66 (1.10–2.50), and 2.31 (1.47–3.65),

Table 1. Baseline characteristics according to categories of systolic blood pressure and body mass index

	Systolic BP categories[a]			Body mass index categories[b]		
	Normal SBP	Systolic prehypertension	Systolic hypertension	Underweight	Normal weight	Overweight
Number, *n*	2,697	2,201	2,008	548	4,960	1,398
Sex (men, %)	42.3	50.7	50.3	36.2	46.8	51.9
Age, year	49.3±12.3	56.9±11.7	63.5±9.6	56.2±14.8	55.6±12.7	56.7±12.0
Systolic BP, mm Hg	107.1±7.8	128.8±5.7	153.2±16.8	119.4±23.1	126.3±21.1	134.6±21.3
Diastolic BP, mm Hg	69.0±7.8	79.9±8.3	87.8±11.7	71.4±11.9	77.2±11.6	83.2±12.0
Body mass index, kg/m^2	21.7±2.8	22.8±2.9	23.4±3.3	17.4±1.0	21.9±1.7	27.1±2.1
Hypertension, %	0.3	10.9	100.0	20.0	29.7	48.1
Diabetes mellitus, %	2.6	5.0	8.3	3.1	4.1	8.9
Hyperlipidemia, %	28.8	40.5	44.9	36.5	36.4	44.4
Chronic kidney disease, %	6	9	13	9	8	10
Current smoking, %	31.7	27.9	23.7	30.1	28.4	26.4
Current drinking, %	49.7	53.1	49.5	41.6	51.5	51.6
History of stroke, %	0.4	1.0	3.5	1.6	1.4	2.0
History of heart disease, %	0.7	2.1	4.0	1.3	2.1	2.7
Premature contractions, %[c]	1.6	2.3	3.6	3.6	2.3	2.2

Abbreviation: SBP, systolic blood pressure.

[a]Normal SBP, SBP < 120 mm Hg; systolic prehypertension, SBP = 120–139 mm Hg; systolic hypertension, SBP ≥ 140 mm Hg and/or antihypertensive drug users.

[b]Body mass index was categorized by the following criteria: underweight, <18.5 kg/m^2; normal weight, 18.5 to <25 kg/m^2; and overweight, ≥25 kg/m^2.

[c]Premature contractions consist of premature atrial and/or ventricular contractions without atrial fibrillation/flatter at the baseline.